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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,496	11/01/2001	Torben Laesgaard Nissen	0218us210	7340
30560	7590	03/18/2004	EXAMINER	
MAXYGEN, INC. INTELLECTUAL PROPERTY DEPARTMENT 515 GALVESTON DRIVE RED WOOD CITY, CA 94063			MERTZ, PREMA MARIA	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/003,496	Applicant(s) NISSEN ET AL.	
	Examiner Prema M Mertz	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above claim(s) 28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-27 and 29-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-27, 29-33) on 1/9/2004 is acknowledged.

Claim 28 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It is suggested that the title be changed to recite "single-chain G-CSF polypeptides".

Claim Rejections - 35 USC § 112, first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-6, 8-11, 14-17, 20-27, 29-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for single-chain multimeric polypeptides comprising hG-CSF protein monomers set forth in SEQ ID NO:1 or single-chain multimeric polypeptides comprising hG-CSF protein monomers of amino acid sequence that differs from that set forth in SEQ ID NO:1 by an amino acid modification as set forth in claim 7 or claim 13, does not reasonably provide enablement for a single-chain multimeric polypeptide having G-CSF activity comprising at least two monomeric units selected from variants of hG-CSF wherein said variant of hG-CSF comprises at least one substitution, addition or deletion compared to SEQ

ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

Claim 1 is overly broad in its limitation of "...variants of hG-CSF " because no guidance is provided as to which of the myriad of polypeptide species encompassed by the claims will retain the characteristics of a human G-CSF polypeptide. Applicants disclose (page 7, lines 11-15) that variants of the monomeric hG-CSF polypeptide can be generated by deletions, insertions, and substitutions without disclosing any actual or prophetic examples on expected performance parameters of any of the possible muteins of the hG-CSF protein molecule. For example, claims 6 and 8, encompass hG-CSF variants having at least one modification and no upper limit on the number of modifications, such that every amino acid residue in hG-CSF can be substituted with another amino acid. However, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals,

erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is no guidance provided in the instant specification as to how one of skill in the art would generate a hG-SCF polypeptide other than the ones recited in claim 7. Applicants have listed in the specification on pages 31-35 various preferred substitutions for muteins of G-CSF with at least one substitution in SEQ ID NO:1. However, the instant specification fails to enable hG-CSF muteins as recited in claim 6 or 8, which muteins encompass unlimited substitutions, deletions and additions to SEQ ID NO:1. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Given the breadth of the claims, in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

The claimed invention encompasses hG-CSF molecules not envisioned or described in the specification, and neither does the specification disclose how these claimed hG-CSF can be distinguished from each other. The specification only enables variant hG-CSF molecules as recited in claims 7 and 13, the polypeptides having specific characteristics and properties. Therefore, it would require undue experimentation to determine which proteins having the biological activity of a hG-CSF protein, would be encompassed by the scope of the claims. The disclosure of the polypeptides of claim 7 and 13 is clearly insufficient support under the first paragraph of 35 U.S.C. § 112. In In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), the Courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Furthermore, the amount of embodiments corresponding to the desirable hG-CSF polypeptides, may be innumerable, and the enabled embodiments amount to only a few. Therefore, there are substantial scientific reasons to doubt the scope of enablement, as set forth above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not enable any other polypeptides other than those in claims 7 and 13, and since it is deemed to constitute undue experimentation to determine all the others, the disclosure is not commensurate with the scope of the claims.

It is suggested that if Applicants are aware of references disclosing which hG-CSF amino acid residues are expendable or substitutable, they provide such references to the Examiner, in the absence of which this rejection will be maintained.

Claim rejections-35 USC § 112, second paragraph

5. Claims 1-27, 29-33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 9, 10, 29, 31 are vague and indefinite because they recite "variant". The metes and bounds of this term are unclear because there is no upper limit on the number of additions, substitutions or deletions to the hG-CSF amino acid sequence set forth in SEQ ID NO:1.

Claims 4-5, 8, recite SEQ ID NO:1 in brackets and this is confusing. It is suggested that that the claims be amended to recite "amino acid sequence of hG-CSF as set forth in SEQ ID NO:1".

Claims 10, 20-21, recite "luciferase assay described herein" which is improper because this is not a positive limitation in the claims. A claim must be complete in itself.

Claim 22 is improper because it fails to recite a "nucleic acid comprising a nucleotide sequence". A nucleotide sequence is a property of a "nucleic acid".

Similarly, claim 23 is improper because it fails to recite "an expression vector comprising a nucleic acid according to". Claim 25 is improper for the same reasons.

Claims 2-3, 6-8, 11-19, 24-27, 30, 32-33 are rejected as vague and indefinite insofar as they depend on the above claims for their limitations.

Claim rejections-35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-27, 29-33 are rejected under 35 U.S.C. § 103 as being unpatentable over Ishikawa et al (US Patent No. 5,824,778) in view of Sytkowski (WO 99/38891).

Ishikawa et al. teaches obtaining recombinant hG-CSF having at least one lysine, aspartic acid or glutamic acid is included (see column 2, lines 7-65), and a PEG covalently bound through amino acid residues of the hG-CSF polypeptide (column 2, last 2 lines) wherein the number of neutrophils in mice injected with the PEG G-CSF are higher than those in mice injected with hG-CSF alone (see column 8, lines 23-60 and Table 2). The reference does not teach at least two monomeric units of hG-CSF which multimers increases hG-CSF circulating half-life.

WO 99/38891 teaches multimeric polypeptides comprising two or more erythropoietin molecules linked together to produce multimeric erythropoietin with a prolonged circulating half-life relative to wild-type erythropoietin (see page 5, lines 1-20). The reference also teaches that the erythropoietin dimmers showed a significantly prolonged circulating half-life *in vivo*, relative to wild-type erythropoietin (page 6, lines 2-5) and that the effective amount of multimeric polypeptides with prolonged circulating half-life requires less frequent administration than equivalent amount of wild-type polypeptide (see page 25, lines 3-15).

Therefore, it would have been obvious to one having ordinary skill in the art to modify the hG-CSF polypeptide of Ishikawa et al. such that it includes the multimers of the monomeric hG-CSF polypeptide bonded to PEG to obtain a multimeric hG-CSF protein with an increased circulating half-life, as taught by Sytkowski, to obtain the known functions and advantages of hG-CSF as per the teachings of Ishikawa. Like erythropoietin, cytokines such as G-CSF are well-known in the art as having a short half-life. Therefore, it would be obvious to obtain multimers of the hG-CSF protein conjugated to PEG, to improve the therapeutic potential of hG-CSF. One would have been motivated to obtain multimers comprising hG-CSF and PEG to decrease its clearance rate *in vivo* and also since the multimer protein would have greater biological activity than

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the same amount of hG-CSF alone. Therefore, lower doses of hG-CSF could be used therapeutically.

With respect to claims 10, 20-21, there would be a reasonable expectation of success by one of skill in the art based on the above references and that an in vitro bioactivity in the range of about 2-30% of the bioactivity of non-conjugated hG-CSF would be obtained because of the size of the PEG molecules which affects the biological activity of hG-CSF (steric hindrance caused by the molecular weight of PEG which masks the active site of hG-CSF).

Therefore, based on the references, it would have been obvious to construct multimers of hG-CSF linked to PEG to obtain a long-lived molecule because it is well known in the art that PEG and multimers of short-lived molecules are able to increase the stability of rapidly cleared molecules.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 271-0871.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz
Prema Mertz Ph.D.

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Primary Examiner
Art Unit 1646
March 4, 2004